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(54) Title: METHACRYLATE BACKBONE SURFACTANTS IN NANOPARTICULATE FORMULATIONS

(57) Abstract

Nanoparticles having an effective average particle size diameter of less than 100 nm comprising a crystalline organic drug substance and a copolymer of methoxypolyethyleneglycol-methacrylate-methoxymethacrylate adsorbed on the surface of the crystalline organic drug substance.

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METHACRYLATE BACKBONE SURFACTANTS IN NANOPARTICULATE FORMULATIONS

Field of the Invention

This invention is directed to nanoparticles containing a diagnostic or therapeutic agent and a methacrylate backbone polymer associated therewith.

Background Of The Invention

Nanoparticles, described in U.S. Patent No. 5,145,684, are particles consisting of a poorly soluble therapeutic or diagnostic agent onto which are adsorbed a non-crosslinked surface modifier, and which have an average particle size of less than about 400 nanometers (nm).

Such nanoparticles are extremely valuable in the field of both diagnostic imaging and therapeutics as will be pointed out hereunder.

a) Diagnostic Agents

X-Ray imaging is a well known and extremely valuable tool for the early detection and diagnosis of various disease states in the human body. The use of contrast agents for image enhancement in medical x-ray imaging procedures is widespread. An excellent background on contrast agents and media in medical imaging is provided by D.P. Swanson et al., *Pharmaceuticals in Medical Imaging*, 1990, MacMillan Publishing Company, the disclosure of which is hereby incorporated by reference in its entirety.

Briefly, in x-ray imaging, transmitted radiation is used to produce a radiograph based upon overall tissue attenuation characteristics. X-rays pass through various tissues and are attenuated by scattering, i.e., reflection or refraction or energy absorption. However, certain body organs, vessels and anatomical sites exhibit so little absorption of x-ray radiation that radiographs of these body portions are difficult to obtain. To overcome this problem, radiologists routinely introduce an x-ray absorbing medium containing a contrast agent into such body organs, vessels and anatomical sites.

Currently available x-ray contrast agents generally exhibit a lack of site directed delivery or compartmentalization. Consequently, large quantities of agent are normally required for imaging. It would be desirable to restrict the contrast agent to specific biological or anatomical compartments, such as the blood pool, liver, kidney or spleen. This would reduce the overall amount of agent which needs to be administered to achieve the desired contrast enhancement.

Maximum enhancement of major blood vessels takes place during the so-called vascular phase of contrast media kinetics which occurs within about the first two minutes following the intravascular infusion or bolus injection of the contrast media. This is because the plasma concentration of an intravascular contrast medium decreases rapidly as a result of vascular mixing transcapillary diffusion of the medium from the circulation into the interstitial spaces and renal excretion. Consequently, imaging of blood vessels must take place within a narrow time window, typically within a few minutes after infusion or injection of the x-ray contrast agent. Currently, there is no commercially available x-ray contrast agent for imaging blood vessels which provides good contrast images of the vasculature for an extended period of time. Therefore, multiple injections are often required to visualize the vasculature adequately. Furthermore, arteriography, as currently practiced, typically requires percutaneous or surgical catheterization, fluoroscopic localization and multiple bolus arterial administrations to adequately visualize a given vascular region.

The need for improved visualization of the liver, kidney and spleen, particularly for early detection of metastases, has led to numerous attempts at developing a contrast medium for accumulation by the mononuclear phagocyte system (MPS). In *Handbook of Experimental Pharmacology,* Vol. 73, Radiocontrast Agents, Chapter 13, "Particulate Suspensions as Contrast Media", Violante and Fischer describe and analyze the problems and complexities involved in designing and formulating such a medium. Inasmuch as the MPS of the liver and spleen is known to trap particles by phagocytosis, contrast agents in particulate form, such as emulsions of iodinated oils, e.g., iodinated ethyl esters of poppy seed oil, and liposomes containing water-soluble iodinated contrast agents have been proposed for liver and spleen visualization. However, emulsions tend to be unacceptably toxic when administered both intravenously and subcutaneously and liposomes tend to require unacceptably large amounts of lipid to achieve adequate contrast enhancement. The MPS or Kuppfer cells of the liver, to which liposomes and emulsions have been directed, constitute approximately 5 percent of the total cell population, the remainder being hepatocyte cells.

Submicron inorganic radioactive thorium dioxide particles have been used for liver visualization and have shown effective contrast enhancement in clinical testing. However, their use has been discontinued because of the extremely lengthy retention of the particles in e liver. This , in combination with the inherent

radioactivity of thorium, has led to serious adverse side effects including neoplasm and fibrosis.

Violante et al, U.S. Patent No. 4,826,689, disclose a method of making uniformly sized noncrystalline amorphous particles from water-insoluble organic compounds wherein the organic compound is dissolved in an organic solvent. In one embodiment, iodipamide ethyl ester is dissolved in dimethylsulfoxide. However solvent precipitation techniques such as described in U.S. Patent No. 4,826,689 for preparing particles tend to provide solvent contaminated particles. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels for diagnostic imaging. Additionally, amorphous materials and formulations tend to exhibit unacceptably poor stability and/or short shelf-lives.

Motoyama et al, U.S. Patent No. 4,540,602 disclose that a solid drug can be pulverized in an aqueous solution of a water-soluble high molecular substance, and that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 μm or less to 5μm in diameter. However, there is no suggestion that particles having an average particle size of less than about 400 nm can be obtained. Indeed, attempts to reproduce the wet grinding procedures described by Motoyama et al resulted in particles having an average particle size of much greater than 1 μm.

PCT/EP90/00053 describes water-insoluble iodinated carbonate esters reported to be useful as contrast agents for visualization of the liver and spleen. Particles of mean diameter on the order of 1.0 micron of the disclosed esters reportedly are taken up by the reticuloendothelial system of the liver and spleen. However, such particles are prepared by conventional mechanical crushing or spray drying techniques or by solvent precipitation techniques such as described in U.S. Patent No. 4,826,689.

b. Therapeutics

Bioavailability is the degree to which a drug becomes available to the target tissue after administration. Many factors can affect bioavailability including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/ml, tend to be eliminated from the gastrointestinal

tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling, as discussed by Lachman et al, *The Theory and Practice of Industrial Pharmacy,* Chapter 2, "Milling", p. 45, (1986), the limit of fineness is reached in the region of 100 microns (100,000 nm) when material cakes on the milling chamber. Lachman et al note that wet grinding is beneficial in further reducing particle size, but that flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). However, there tends to be a bias in the pharmaceutical art against wet milling due to concerns associated with contamination. Commercial airjet milling techniques have provided particles ranging in average particle size from as low as about 1 to 50 μm (1,000 - 50,000 nm). However, such dry milling techniques can cause unacceptable levels of dust.

EPO 275,796 describes the production of colloidally dispersible systems comprising a substance in the form of spherical particles smaller than 500 nm. However, the method involves a precipitation effected by mixing a solution of the substance and a miscible non-solvent for the substance and results in the formation of non-crystalline nanoparticles. Furthermore, precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical.

U.S. Patent No. 5,145,684 discloses a process for preparing particles consisting of a crystalline drug substance having a surface modifier or surface active agent adsorbed on the surface of the particles in an amount sufficient to maintain an average particle size of less than about 400 nanometers. The process of preparation comprises the steps of dispersing the drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to an average particle size of less than 400 nm. The particles can be reduced in the presence of a

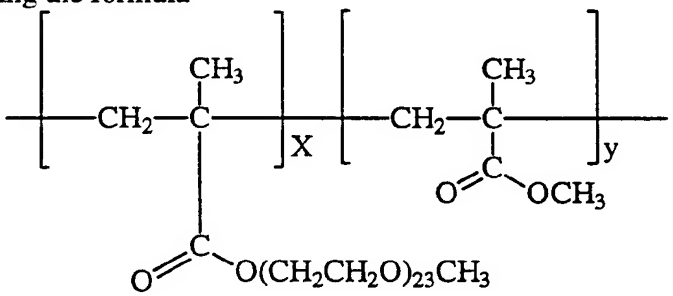
surface active agent or, alternatively, the particles can be contacted with a surface active agent after attrition. The presence of the surface active agent prevents flocculation/agglomeration of the nanoparticles.

We have now discovered that both poorly soluble crystalline drug substances and poorly soluble crystalline diagnostic agents can be made into nanoparticles having an effective average particle size diameter of less than 100 nm.

Summary Of The Invention

In accordance with the present invention nanoparticulates having an effective average particle size diameter of less than 100 nm are provided comprising:

(a) 99.9 to 10% by weight of a crystalline organic substance having a solubility in water of less than 10 mg/ml, said crystalline organic substance having a (b) copolymer of a methoxypolyethyleneglycol-methacrylate-methoxymethacrylate adsorbed on the surface thereof in an amount of 0.1 to 90% by weight, said copolymer having the formula



wherein the ratio of x:y is from about 1:1 to about 3:1, and preferably of from about 2.5:1, and having an average molecular weight of from about 50,000 to about 150,000 daltons, and preferably of from about 80,000 to about 100,000 daltons, in combination with a pharmaceutically acceptable carrier.

The organic crystalline substance may be a therapeutic or a diagnostic x-ray contrast agent.

Detailed Description Of The Invention

This invention is based partly on the discovery that drug particles having an extremely small effective average particle size can be prepared by milling in the presence of grinding media in conjunction with a a copolymer of methoxypolyethyleneglycol-methacrylate-methoxymethacrylate, and that such

particles are stable and do not appreciably flocculate or agglomerate due to interparticle attractive forces and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability. While the invention is described herein primarily in connection with its preferred utility, i.e., with respect to nanoparticulate drug substances for use in pharmaceutical compositions, it is also believed to be useful in other applications such as the formulation of particulate cosmetic compositions and the preparation of particulate dispersions for use in image and magnetic recording elements.

The particles of this invention comprise a drug substance. The drug substance exists as a discrete, crystalline phase. The crystalline phase differs from a non-crystalline or amorphous phase which results from precipitation techniques, such as described in EPO 275,796 cited above.

The invention can be practiced with a wide variety of drug substances. The drug substance preferably is present in an essentially pure form. The drug substance must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble" it is meant that the drug substance has a solubility in the liquid dispersion medium, e.g. water, of less than about 10 mg/ml, and preferably of less than about 1 mg/ml. A preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid media in which a drug substance is poorly soluble and dispersible including, for example, aqueous salt solutions, safflower oil and solvents such as ethanol, t-butanol, hexane and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art.

Suitable drug substances can be selected from a variety of known classes of drugs including, for example, analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones (including steroids), anti-allergic agents,

stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines. Preferred drug substances include those intended for oral administration and intravenous administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, *The Extra Pharmacopoeia,* Twenty-ninth Edition, The Pharmaceutical Press, London, 1989, the disclosure of which is hereby incorporated herein by reference in its entirety. The drug substances are commercially available and/or can be prepared by techniques known in the art.

Representative illustrative species of drug substances useful in the practice of this invention include:

17-a-pregno-2,4-dien-20-yno-[2,3-d]-isoxazol-17-ol (Danazol);
5a,17a,-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17-ol (Steroid A);
piposulfam;
piposulfan;
camptothecin;
ethyl-3,5-diacetoamido-2,4-6-triiodobenzoate (WIN 8883);
ethyl(3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy)acetate (WIN 12901),
ethyle-2-(bis(acetylamino)-2,4,6-triiodobenzoyloxy)butyrate (WIN 16318),
6-ethoxy-6-oxohexyl-3,5,-bis(acetylamino)-2,4,6-triiodobenzoate (WIN 67722).

Other suitable agents are described in U.S. Patent Nos. 5,260,478 and 5, 264,610.

In particularly preferred embodiments of the invention, the drug substance is a steroid such as danazol or Steroid A or an antiviral agent.

The particles of this invention contain a discrete phase of a drug substance as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the drug substance but do not chemically bond to the drug.

The surface modifier of the present invention is the above-specified copolymers of methoxypolyethyleneglycol-methacrylate-methoxymethacrylate. The discovery for the utilization of this surface modifier is based on the unexpected finding that its use on the surface of drug particles allows the preparation and maintenance of such particles in a much reduced particle size range as compared to the use of other surface modifiers, such as disclosed in U.S. Patent No. 5,145,684.

The surface modifier is adsorbed on the surface of the drug substance in an amount sufficient to maintain an effective average particle size of less than about 100 nm. The surface modifier does not chemically react with the

drug substance or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 100 nm" it is meant that at least 50% of the particles have a weight average particle size of less than about 100 nm when measured by the above-noted techniques.

The particles of this invention can be prepared in a method comprising the steps of dispersing a drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to an effective average particle size of less than about 100 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention is set forth below. The drug substance selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse drug substance selected be less than about 100 μm, as determined by sieve analysis. If the coarse particle size of the drug substance is greater than about 100 μm then it is preferred that the particles of the drug substance be reduced in size to less than 100 μm using a conventional milling method such as airjet or fragmentation milling.

The coarse drug substance selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the drug substance in the liquid medium can vary from about 0.1 - 60% and preferably is from 5 - 30% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can vary from about 0.1 to 90%, and preferably is 1 - 75%, more preferably 20 - 60%, by weight based on the total combined weight of the drug substance and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise.

The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 100 nm. It is preferred that the premix be used directly when a ball mill is used for attrition.

Alternatively, the drug substance and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the particle size of the drug substance conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, and media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 100 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle fragmentation and media erosion.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. We have found that zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. However, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 3 g/cm^3.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the drug substance. Processing temperatures of less than about 30 - 40°C are ordinarily preferred. If desired, the processing equipment can

be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Processing pressures up to about 20 psi (1.4 kg/cm^2) are typical of media milling.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g., by shaking vigorously. Optionally, the dispersion can be subjected to a sonication step, e.g., using an ultrasonic power supply. For example, the dispersion can be subjected to ultrasonic energy having a frequency of 20 - 80 kHz for a time of about 1 to 120 seconds.

The relative amount of drug substance and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular drug substance. The surface modifier preferably is present in an amount of about 0.1-10 mg per square meter surface area of the drug substance. The surface modifier can be present in an amount of 0.1-90%, preferably 20-60% by weight based on the total weight of the dry particle.

The resulting dispersion of this invention is stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of surface modified drug nanoparticles can be spray coated onto sugar spheres or onto a pharmaceutical excipient in a fluid-bed spray coater by techniques well known in the art.

Pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. These include non-toxic physiologically acceptable carriers, adjuvants or vehicles for parenteral injection, for oral administration in solid or liquid form, for rectal administration, and the like. A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described pharmaceutical composition. The selected dosage level of the drug substance for treatment is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore, depends upon the particular drug substance, the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors. As noted, it is a particularly

advantageous feature that the pharmaceutical compositions of this invention exhibit unexpectedly high bioavailability as illustrated in the examples which follow. Furthermore, it is contemplated that the drug particles of this invention provide more rapid onset of drug action and decreased gastrointestinal irritancy.

It is contemplated that the pharmaceutical compositions of this invention will be particularly useful in oral and parenteral, including intravenous, administration applications. It is expected that poorly water soluble drug substances, which prior to this invention, could not have been administered intravenously, may be administered safely in accordance with this invention. Additionally, drug substances which could not have been administered orally due to poor bioavailability may be effectively administered in accordance with this invention.

While applicants do not wish to be bound by theoretical mechanisms, it is believed that the surface modifier hinders the flocculation and/or agglomeration of the particles by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation.

The following examples will further illustrate the invention.

Example 1

Samples were prepared for comparing mean particle size. Each of the samples contained 15% w/v of WIN 8883 and 4% w/v of a surfactant in deionized water.

Three 6% w/v stock solutions were prepared by dissolving 600 mg of:

(a) the copolymer methoxypolyethyleneglycol-methacrylate-methoxymethacrylate having a molecular weight of 94,000 daltons [hereinafter sometimes referred to as PEG-methacrylate copolymer],

(b) F108 and

(c) T908

in 10 ml of deionized water.

To each of three 15 ml bottles (Samples 1, 2 and 3) 7.5 ml of $ZrSiO_4$ beads having a size of 1.1 mm and 562 mg of WIN 8883 were added. Then 2.5 ml of stock solution (a) and 0.994 ml of deionized water were added to Sample 1; 2.5 ml of stock solution (b) and 0.994 ml of deionized water were added

to Sample 2; and 2.5 ml of stock solution (c) and 0.994 ml of deionized water were added to Sample 3.

The sample bottles were sealed and placed on a roller mill running at 160 rpm for 5 days. At the end of day 5, aliquots of the samples were diluted 100 fold with deionized water for particle size measurement. The results were as follows:

Sample	Surfactant	Mean Particle Size (Nm)
1	PEG-methacrylate copolymer	68
2	F108	130
3	T908	241

Example 2

Two samples were prepared each containing in deionized water 10% w/v of an elastase inhibitor and 2.5 ml of 0.5 mm polystyrene beads. To Sample, 1 25 ml of a 3% w/v solution PEG-methacrylate copolymer in deionized water was added while to Sample 2, 25 ml of a 3% w/v solution of F68 surfactant in deionized water was added. The samples were then milled in a 100 ml polycarbonate centrifuge tube on a DC mill for 4 hrs at 2300 rpm. At the end of 4 hrs aliquots of the samples were diluted 100 fold with deionized water for particle size measurement. The results were as shown.

Sample	Surfactant	Mean Particle Size (Nm)
1	PEG-methacrylate copolymer	120
2	F68	193

Example 3

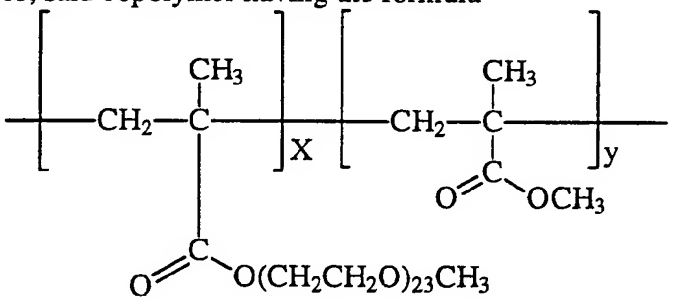
An aliquot of the Sample 1 of Example 1 was dried under stream of nitrogen to provide a thin film. Scanning electron microscopic examination revealed the embedded nano-WIN 8883 particles. Due to the adhesive nature of the PEG-methacrylate copolymer the nanoparticle-containing film can be used as a bioadhesive for oral delivery of a drug or as skin patches.

It will be understood that variations and modifications of the invention described can be effected within the spirit and scope of the invention.

What Is Claimed Is:

1. Nanoparticles having an effective average particle size diameter of less than 100 nm comprising:

(a) 10 to 99.9% w/w of a crystalline organic substance and (b) 0.1 to 90% w/w of a copolymer of methoxypolyethyleneglycol-methacrylate-methoxymethacrylate adsorbed on the surface of said crystalline organic substance, said copolymer having the formula



wherein the ratio of x:y is from about 1:1 to about 3:1.

2. The nanoparticles of claim 1 wherein the average molecular weight of said copolymer is from about 50,000 to about 150,000 daltons.

3. The nanoparticles of claim 1 wherein the average molecular weight of said copolymer is from about 80,000 to about 100,000 daltons.

4. The nanoparticles of claim 1 wherein the ratio of x:y is from about 2.5:1.

5. The nanoparticles of claim 1 wherein said drug substance is selected from the group consisting of: analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, contrast media, corticosteroids, cough suppressants, diuretics, dopaminergics, haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, sympathomimetics, thyroid agents, vasodilators and xanthines.

6. A stable dispersion consisting essentially of a liquid dispersion medium and the particles of claim 1.

7. The dispersion of claim 6 wherein said dispersion medium is water.

8. The dispersions of claim 6 wherein said dispersion medium is selected form the group consisting of safflower oil, ethanol, t-butanol, hexane and glycol.

9. A pharmaceutical composition comprising the particles of claim 1 and a pharmaceutically acceptable carrier thereof.

10. A method of treating a mammal comprising the step of administering to the mammal an effective amount of the pharmaceutical composition of claim 9.